ABSTRACTS

Abstracts of Original Contributions: Young Investigators Awards Competition

The purpose of the Awards is to find and encourage the Young Investigators of promise on whom the future of cardiology depends. Any physician/scientist who is currently in a residency or fellowship training program or who has been in such a program within the past 3 years is eligible to submit an original investigation. Medical students and PhD candidates are also eligible for the competition.

The Judging Committee will select a first and second place winner and three honorable mentions for each of the following categories: a) Clinical Investigations; b) Physiology, Pharmacology, and Pathology; and c) Molecular and Cellular Cardiology. The Awards will be presented at the 47th Annual Convocation Ceremony on Wednesday, April 1, at 6:00 pm. The Young Investigator of the Year (first place) for each category will receive a plaque, a certificate and $2,000. Second place winners each receive a certificate and a check for $1,000. The three honorable mentions each receive a certificate and a check for $500.

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Timothy J. Gardner, MD, FACC
Chair
1998 Young Investigators Awards Committee

406 Young Investigators Awards Competition – Physiology, Pharmacology, and Pathology

Monday, March 30, 1998 10:30 a.m.–Noon
Georgia World Congress Center, Room 364W

10:30

406-1 Dichotomous Roles for Inducible Nitric Oxide Synthase During Cardiac Allograft Rejection

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To evaluate the role of NOS2 in acute and chronic rejection, we studied cardiac allografts with ongoing NOS2-deficiency using recipient mice with targeted gene deletion. We compared graft function (ventricular contractility) and histologic outcome (parenchymal and vascular rejection) in NOS2-deficient and wild type recipients. In non-immunosuppressed transplants undergoing acute rejection, ventricular function reflected by palpation scores (scale 0-4) was comparably reduced to 1.1 ± 0.7 in NOS2−/− recipients (n = 7) and to 0.6 ± 0.4 in wild type recipients (n = 10, p = 0.07). However, mean rejection scores (ISHLT score 0–4) were significantly lower in grafts from NOS2-deficient recipients (1.8 ± 1.2 compared to 3.1 ± 0.7 in wild type recipients, p < 0.05). This effect was associated with reduced apoptotic activity as assessed by DNA fragmentation (anti-nucleosome-ELISA) and mRNA regulation of ICE (^{32}P-RT-PCR). In contrast, in immunosuppressed transplants (anti-CD4 and -CD8) undergoing chronic rejection mean palpation scores were significantly reduced in NOS2−/− recipients (0.3 ± 0.5, n = 12) compared to wild type recipients (2.3 ± 1.0, n = 8, p < 0.0001). Rejection scores were significantly higher in NOS2−/− recipients (3.8 ± 0.3 versus 1.8 ± 0.6 in wild type recipients, p < 0.0001). Computer-assisted analysis of all elastin-stained vessels (n = 234) showed a significant increase in severity of luminal occlusion in allografts from NOS2−/− recipients (77.1 ± 9.4% occlusion) compared to those from wild type recipients (40.8 ± 13.6%, p < 0.0001). This was associated with an increased contribution of α-smooth muscle actin positive cell area to the expanded neointima in NOS2−/− recipients (28.2 ± 2.0% versus 13.2 ± 2.3%, p < 0.0001).

Hence, NOS2 accelerates acute rejection but delays chronic rejection. Promotion of acute rejection involves apoptotic tissue damage. Prevention of chronic rejection involves an anti-arteriosclerotic effect disrupting myointimal thickening.

10:45

406-2 Expression of Two K^+ Families Regulates the Excitability of Small Coronal Arteries From Human Left Ventricle

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Potassium channels in vascular smooth muscle (VSM) membranes play a pivotal role in regulating arterial tone. Surprisingly, the identity of the K^+ channels which regulate the excitability of small human coronary arteries is unknown. Thus, we dissected small arteries from left ventricles of explanted human hearts for use in patch-clamp recordings, Western immunoblotting and microvessel perfusion studies. In patch-clamp experiments using single VSM cells, a Ca^{2+}-activated K^+ current (K_{Ca}) blocked by iberiotoxin, and a voltage-gated K^+ current (K_V) sensitive to block by 4-aminopyridine, accounted for the majority of the observed K^+ current at physiological membrane potentials. Subsequently, Western analysis using sequences-specific antibodies directed against the α-subunit (pore-forming subunit) of the K_{Ca} channel and two K_V channel subfamilies confirmed their expression in human coronary VSM membranes. Finally, we examined the functional role of K_{Ca} and K_V channels in isolated segments of small human coronary arteries, which were cannulated on glass micropipettes and perfused at an intraluminal pressure of 80 mmHg. Diameters were monitored by video-microscopy and the membrane potentials were measured by microelectrodes. Under resting conditions, arteries showed an internal diameter of 334 ± 28 μm (n = 9), and resting membrane potentials in a subset of 3 vessels averaged −49 ± 1 mV. Superfusion with iberiotoxin (100 nmol/L) to block K_{Ca} channels, or with 4-aminopyridine to block K_V channels, markedly depolarized the coronary VSM cells by about 15 mV and constricted arteries by 63 ± 19 μm and 61 ± 7 μm, respectively (n = 6–7). These results provide initial evidence for an important role of K_{Ca} and K_V channels in regulating the reactivity of small human coronary arteries. Further molecular identification of these K^+ channels may assist in designing new therapies to optimize blood flow to the human myocardium.